REPORT

WHO Technical Consultation on Neonatal Vitamin A Supplementation Research Priorities

Geneva, Switzerland, 4-5 December 2008

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Declarations of Interest

Participants of the WHO Technical Consultation on Neonatal Vitamin A Supplementation Research Priorities reported the following:

Emily Wainwright reported being employed by an organization (USAID) that provided financial support to some of the research trials presented during the meeting.

Professor Keith P West Jr reported receiving a DSM, Ltd scholarship in micronutrient deficiency prevention that is awarded to one student each year in the Program for Human Nutrition at Johns Hopkins School of Public Health, where he is affiliated.

The other participants declared they had no conflicts of interest.

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1. Introduction

Vitamin A supplementation has been promoted as an essential child survival intervention for children 6-59 months of age. Studies that evaluated the effects of vitamin A supplementation in the 1-5 month period did not show any child survival benefits. Recently, there has been considerable interest in vitamin A supplementation during the neonatal period (0-28 days) with three trials, conducted in Indonesia, India, and Bangladesh, showing a reduction in mortality during infancy ranging from 15-64%. However, three other trials conducted in Nepal, Zimbabwe and Guinea-Bissau have shown no effect of this intervention on infant mortality, regardless of when vitamin A was given in the neonatal period.

In order to better understand these apparently contradictory results, a sytematic review of randomized controlled trials (RCT) was commissioned by the World Health Organization's (WHO) Department of Child and Adolescent Health and Development (WHO/CAH) and Department of Nutrition for Health and Development (WHO/NHD) to evaluate the effects of neonatal vitamin A supplementation on infant mortality, morbidity and adverse effects. The authors of this systematic review concluded that vitamin A supplementation during the neonatal period (0-28 days) was not associated with a reduced risk of infant mortality and morbidity and identified several issues that needed further research. WHO (CAH and NHD Departments) jointly with UNICEF (Nutrition Section) convened a Technical Consultation to discuss the WHO-commissioned systematic review and identify priorities for future research on neonatal vitamin A supplementation.

Objectives of the meeting

i. To review the findings of the WHO-commissioned systematic review.
ii. To identify and discuss research gaps in the use of vitamin A supplements for neonates.
iii. To prioritize the research needs.

Expected outputs of the meeting

i. List of research priorities for neonatal vitamin A supplementation.
ii. Recommendations for appropriate study design and methodology for the identified research priorities.
iii. Identification of potential academic and research institutions to implement priority research studies.

2. Neonatal Vitamin A Supplementation for the Prevention of Mortality and Morbidity in Infancy: Systematic Review of Randomized Controlled Trials (RCT)

(Presented by HPS Sachdev)

The systematic review was commissioned by WHO's Departments of Child and Adolescent Health and Development, and Nutrition for Health and Development, and conducted by Dr Siddhartha Gogia and Dr HPS Sachdev. The authors declared that they have no conflicts of interest. The authors alone are responsible for the views and conclusions expressed in this review which do not necessarily represent the decisions or policies of WHO.

The objectives of the systematic review were to evaluate the effect of prophylactic, synthetic vitamin A supplementation initiated in the neonatal period (< 1 month of age) on mortality and morbidity during infancy, and assess early adverse effects of this intervention. Randomized or quasi-randomized placebo-controlled trials, with randomization at the individual or cluster level, were eligible for inclusion. Trials conducted only on selected subgroups of neonates, such as those who were of very low birth weight (<1500 grams), HIV-positive, born to known HIV-positive mothers, or sick or hospitalized, were excluded. The comparison group was that in which placebo was administered to the neonate and either placebo or no supplementation was given to the mother during pregnancy or the postpartum period. The primary outcome measures were all-cause mortality during the period between initiation of the intervention and the last follow-up within the age of one year, and all-cause mortality during the neonatal period. Secondary outcome measures included cause-specific mortality, presence of diarrhoea; acute respiratory infection or respiratory difficulty; cough or running nose; fever and vomiting; clinic visits or hospitalizations in the period between initiation of intervention and the last follow-up within the age of one year; and early adverse effects including bulging fontanel; vomiting; irritability; diarrhoea; or fever within one week after receiving the intervention.

A search strategy included computerized bibliographic medical databases and clinical trials websites until July 2008 with no language restrictions. Subgroup analyses were performed only for the primary outcome on prespecified characteristics. For computing the summary relative risk (RR), individual study RR and 95% confidence interval (CI) or standard error (SE) for intention to treat analysis was used if stated by authors, or was computed from the data in the publication, when available. For cluster-randomized trials, the stated cluster adjusted RR and 95% CI were used, irrespective of the method employed. In factorial trials and in multi-arm designs having two or more vitamin A intervention groups, the data in the intervention groups were pooled and compared against the single control group to prevent unit-of-analysis error. Pooled estimates were computed using both fixed effects and random effects model assumptions and the contribution of baseline characteristics to heterogeneity was explored by meta-regression.

Of the 72 references identified through the search strategy, 11 references corresponding to six trials were included (six trials provided mortality data, three trials had relevant morbidity data, and six trials provided adverse effects data). There was no evidence of publication bias (Egger's method, P for bias=0.931). Data from six trials involving 42 508 infants suggest that *there is no evidence of a reduced risk of mortality due to any cause during the first year of life in infants who were supplemented with vitamin A during the neonatal period in comparison to those who received placebo; pooled RR 0.92 (95% CI 0.75 to 1.12, P=0.393; I^2=54.1%, P=0.053) by random effects model (Figure 1).* The pre-specified sensitivity, subgroup, and meta-regression analyses for RR of all-cause mortality during infancy did not identify a consistent significant predictor of mortality during infancy. A stratified analysis of the limited data (three trials) suggests a greater reduction in infant mortality in infants from mothers who had reported night blindness most frequently (mothers with a reported prevalence of 5% or more versus those with less than 5% prevalence of night blindness).

Combined results from the three trials that had information on neonatal mortality (Indonesia, Guinea-Bissau and Bangladesh) suggest that neonates who received the vitamin A supplements were as likely to die during the neonatal period as those who received placebo (pooled RR for neonatal mortality 0.90, 95% CI 0.75 to 1.08). There was no evidence of an increased risk of early adverse effects, including bulging fontanel. The limited data available did not indicate a reduced risk of cause-specific mortality, morbidities (diarrhoea and others), and hospitalization; however, they do suggest an increased risk of acute respiratory infection and a reduced risk of clinic visits.

Some limitations of this review merit consideration. For example, all trials were conducted in developing countries and there were limited data on some high-risk groups (prevalence of maternal night blindness ≥5% and low-birth-weight infants). Also, follow-up duration was variable in the included studies, which precluded constitution of a uniform measure to explore baseline mortality as a predictor. Finally, multiple subgroup and meta-regression analyses were performed, with the possibility of false positive results.

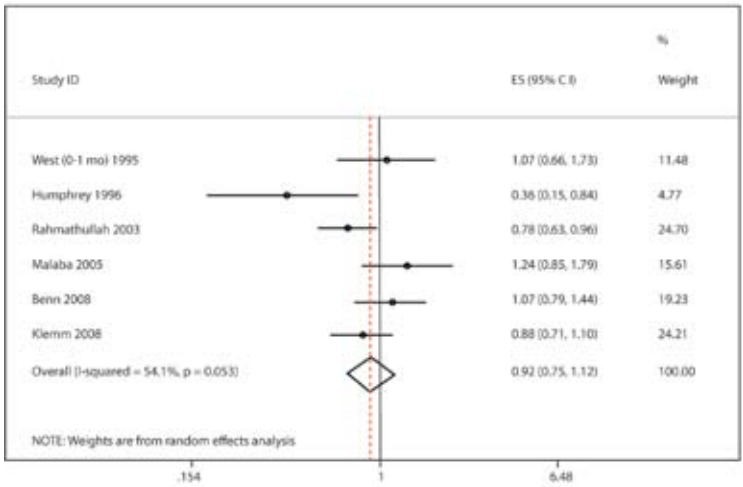

Figure 1. Forest plot of relative risk of mortality during infancy in the intervention group (neonatal vitamin A supplementation) compared with placebo

Sensitivity analysis performed by altering the methodological decisions showed that the results related to the primary outcome were stable, e.g. changing the comparison group to the infants that received placebo irrespective of maternal supplementation status (RR 0.89; 95% CI 0.76 to1.06); changing the outcome to mortality within the first six months (RR 0.91; 95% CI 0.76 to 1.09); or analysing the outcomes when the vitamin A supplementation intervention was provided only during the first 48 hours (RR 0.90; 95% CI 0.73 to 1.12) or during the first week of life (RR 0.90; 95% CI 0.73 to 1.11). Even in the absence of underlying biological plausibility, when the subgroup analysis was done by region, it was not found to be a significant predictor of heterogeneity (P=0.133) on meta-regression although the effect sizes appeared disparate (RR 1.13, 95% CI 0.90 to 1.43, I^2=0% in Africa and RR 0.82, 95% CI 0.66 to 1.02, I^2=45% in Asia).